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ATTY. DOCKET NO. 85761-28

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In re Patent Application of Claire DUBOIS

Serial No. 09/885,914

Group Art Unit: 1614

Filed: June 22, 2001

Examiner:

For: **USE OF FURIN AND FURIN-LIKE PROTEASE INHIBITORS IN THE  
TREATMENT OF INFLAMMATORY OR MATRIX REMODELLING DISEASES**

**INFORMATION DISCLOSURE STATEMENT**

This Information Disclosure Statement is being filed in the manner prescribed by 37 CFR 1.97(b) - (d) to satisfy the duty under 37 CFR 1.56 to disclose to the Office information, known to individuals associated with the filing and prosecution of the subject application, which is material to the examination of the application.

In accordance with 37 CFR 1.97(g) and (h), this statement is not to be construed as a representation that a search has been made or an admission that the information cited herein is, or is considered to be, material to patentability as defined in 37 CFR 1.56(b).

This information disclosure statement is being filed within three months of the filing date of a national application, within three months of the date of entry of the national stage as set forth in 37 CFR 1.491 in an international application; or before the mailing date of a first official action on the merits and therefore applicant respectfully requests consideration under 37 CFR 1.97(b).

In compliance with 37 CFR 1.98(a)(1), a list of all patents, publications or other information submitted for consideration by the Office is hereby provided by way of the attached Form PTO 1449.

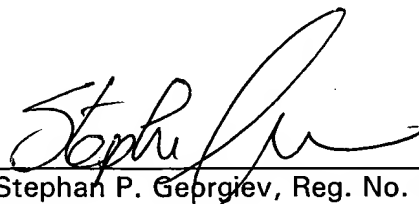
In compliance with 37 CFR 1.98(a)(2), also enclosed is a legible copy of:

- i) each United States and foreign patent;
- ii) each publication or that portion which caused it to be listed; and
- iii) all other information or that portion which caused it to be listed, excluding any copies of a United States patent application.

It is respectfully requested that the information be expressly considered by the Examiner and that the references be made of record and appear among the "References Cited" on any patent to issue therefrom.

The Patent Office is hereby authorized to charge any deficiency, or credit any overpayment in fees to Deposit Account Number 19-2550.

Respectfully submitted,



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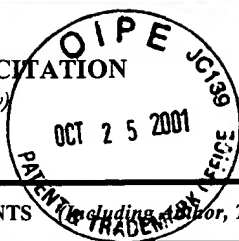
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Encls: Form PTO-1449  
All references listed on Form PTO-1449  
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# INFORMATION DISCLOSURE CITATION

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*EXAMINER INITIAL	OTHER DOCUMENTS (including Abstract, Title, Date, Pertinent Pages, Etc.)
3.	Molloy, S.S., Thomas, L., VanSlyke, J.K., Stenberg, P.E., and Thomas, G. 1994. Intracellular trafficking and activation of the furin proprotein convertase: localization to the TGN and recycling from the cell surface. EMBO J. 13:18-33.
4.	Molloy, S.S., Anderson, E.D., Jean, F., and Thomas, G. 1999. Bi-cycling the furin pathway: from TGN localization to pathogen activation and embryogenesis. Trends Cell. Biol. 9:28-35.
5.	Takahashi, S., Hatsuzawa, K., Watanabe, T., Murakami, K., and Nakayama, K. 1994. Sequence requirements for endoproteolytic processing of precursor proteins by furin: transfection and in vitro experiments. J. Biochem. 116:47-52.
6.	Betsholtz C, Johnsson A, Heldin CH, Westermarck B, Lind P, Urdea MS, Eddy R, Shows TB, Philpott K, Mellor AL, Knott TJ and Scott J. 1986. cDNA sequence and chromosomal localization of human platelet-derived growth factor A-chain and its expression in tumour cell lines Nature 320 (6064), 695-699.
7.	Collins T, Ginsburg D, Boss JM, Orkin SH, Pober JS 1985. Cultured human endothelial cells express platelet-derived growth factor B chain: cDNA cloning and structural analysis. Nature 316(6030):748-50.
8.	Kingsley D.M. 1994. The TGF-beta superfamily: new members, new receptors, and new genetic tests of function in different organisms. Genes Dev. 8(2):133-46.
9.	Bergeron F, Leduc R, Day R. 2000. Subtilase-like pro-protein convertases: from molecular specificity to therapeutic applications. J Mol Endocrinol. 24(1):1-22.
10.	Dubois, C.M., Laprise, M.H., Blanchette, F., Gentry, L.E. and Leduc, R. 1995. Processing of transforming growth factor beta precursor by human furin convertase. J. Biol. Chem. 270:10618-24.
11.	Keyszer, G.M., Heer, A.H., and Gay, S. 1994. Cytokines and oncogenes in cellular interactions of rheumatoid arthritis. Stem Cells. 12:75-86.
12.	Remmers, E.F., Sano, H., and Wilder, R.L. 1991. Platelet-derived growth factors and heparin-binding (fibroblast) growth factors in the synovial tissue pathology of rheumatoid arthritis. Sem. Arthritis Rheum. 21:191-199.
13.	Butler, D.M., Leizer, T., and Hamilton, J.A. 1989. Stimulation of human synovial fibroblast DNA synthesis by platelet-derived growth factor and fibroblast growth factor. Differences to the activation by IL-1. J. Immunol. 142:3098-103.
14.	Smith, R.J., Justen, J.M., Sam, L.M., Rohloff, N.A., Ruppel, P.L., Brunden, M.N., and Chin, J.E. 1991. Platelet-derived growth factor potentiates cellular responses of articular chondrocytes to interleukin-1. Arthritis Rheum. 34:697-706.

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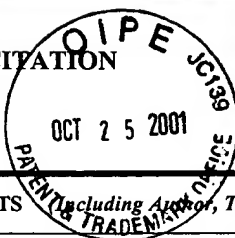
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15. ✓	Wilder, R.L., Case, J.P., Crofford, L.J., Kumkumian, G.K., Lafyatis, R., Remmers, E.F., Sano, H., Sternberg, EM., and Yocum, D.E. 1991. Endothelial cells and the pathogenesis of rheumatoid arthritis in humans and streptococcal cell wall arthritis in Lewis rats. J. Cell. Biochem. 45:162-166.
16. ✓	Reibman, J., Meixler, S., Lee, T.C., Gold, L.I., Cronstein, B.N., Haines, K.A., Kolasinski, S.L., and Weissmann, G. 1991. Transforming growth factor $\beta$ 1, a potent chemoattractant for human neutrophils, bypasses classic signal-transduction pathways. Proc. Natl. Acad. Sci. USA 88:6805-6809.
17. ✓	Brandes, M.E., Mai, U.E., Ohura, K., and Wahl, S.M. 1991. Type I transforming growth factor- $\beta$ receptors on neutrophils mediate chemotaxis to transforming growth factor-beta. J. Immunol. 147:1600-1606.
18. ✓	Wahl, S.M., Hunt, D.A., Wakefield, L.M., McCartney-Francis, N., Wahl, L.M., Roberts, A.B. and Sporn, M.B. 1987. Transforming growth factor type $\beta$ induces monocyte chemotaxis and growth factor production. Proc. Natl. Acad. Sci. USA 84:5788-5792.
19. ✓	McCartney-Francis, N., Mizel, D., Wong, H., Wahl, L., and Wahl, S. 1990. TGF- $\beta$ regulates production of growth factors and TGF- $\beta$ by human peripheral blood monocytes. Growth Factors. 4:27-35.
20. ✓	Wahl SM, Allen JB, Costa GL, Wong HL, Dasch JR.1993. Reversal of acute and chronic synovial inflammation by anti-transforming growth factor $\beta$ . J. Exp. Med. 177:225-30.
21. ✓	Brandes, M.E., Allen, J.B., Ogawa, Y., and Wahl, S.M. 1991. Transforming growth factor $\beta$ 1 suppresses acute and chronic arthritis in experimental animals. J. Clin. Invest. 87:1108-1113.
22. ✓	Black, R.A. et al. 1997. A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells. Nature 385:729-731.
23. ✓	Roghani, M., Becherer, J.D., Moss, M.L., Atherton, R.E., Erdjument-Bromage, H., Arribas, J., Blackburn, R.K., Weskamp, G., Tempst, P., and Blobel, C.P. 1999. Metalloprotease-disintegrin MDC9 : intracellular maturation and catalytic activity. J. Biol. Chem. 274:3531-3540.
24. ✓	Tortorella MD, Burn TC, Pratta MA, Abbaszade I, Hollis JM, Liu R, Rosenfeld SA, Copeland RA, Decicco CP, Wynn R, Rockwell A, Yang F, Duke JL, Solomon K, George H, Bruckner R, Nagase H, Itoh Y, Ellis DM, Ross H, Wiswall BH, Murphy K, Hillman MC Jr, Hollis GF, et al. 1999. Protein, Nucleotide Purification and cloning of aggrecanase-1: a member of the ADAMTS family of proteins. Science. 284(5420):1664-1666.
25. ✓	Abbaszade I., Liu R.Q., Yang F., Rosenfeld S.A., Ross O.H., Link J.R., Ellis D.M., Tortorella M.D., Pratta M.A., Hollis J.M., Wynn R., Duke J.L., George H.J., Hillman M.C. Jr, Murphy K., Wiswall B.H., Copeland R.A., Decicco C.P., Bruckner R., Nagase H., Itoh Y., Newton R.C., Magolda R.L., Trzaskos J.M., et al. Cloning and characterization of ADAMTS11, an aggrecanase from the ADAMTS family. J Biol Chem. 13;274(33):23443-23450.
26. ✓	Massova I, Kotra L.P., Fridman R, Mobashery S. 1998. Matrix metalloproteinases: structures, evolution, and diversification. FASEB J. 12(12):1075-1095.

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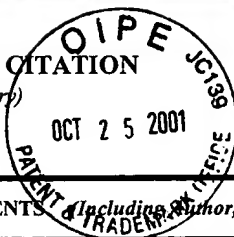
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27. ✓	Pei D. Identification and characterization of the fifth membrane-type matrix metalloproteinase MT5-MMP. 1999. J Biol Chem. 26;274(13):8925-8932.
28. ✓	Schlondorff J, Becherer JD, Blobel CP. 2000. Intracellular maturation and localization of the tumour necrosis factor alpha convertase (TACE). Biochem J. 2000 347:131-138.
29. ✓	Clarke HR, Wolfson MF, Rauch CT, Castner BJ, Huang CP, Gerhart MJ, Johnson RS, Cerretti DP, Paxton RJ, Price VL, Black RA. 1998. Expression and purification of correctly processed, active human TACE catalytic domain in Saccharomyces cerevisiae. Protein Expr Purif. 13(1):104-10.
30. ✓	Maquoi E, Noel A, Franken F, Angliker H, Murphy G, Foidart JM. 1998. Inhibition of matrix metalloproteinase 2 maturation and HT1080 invasiveness by a synthetic furin inhibitor. FEBS Lett. 13;424(3):262-266.
31. ✓	Sato T, Kondo T, Fujisawa T, Seiki M, Ito A. 1999. Furin-independent pathway of membrane type 1-matrix metalloproteinase activation in rabbit dermal fibroblasts. J Biol Chem. 274(52):37280-37284.
32. ✓	Paleolog, E. 1997. Target effector role of vascular endothelium in the inflammatory response: insights from the clinical trial of anti-TNF alpha antibody in rheumatoid arthritis. Mol. Pathol. 50:225-233.
33. ✓	Moreland, L.W., Baumgartner, S.W., Schiff, M.H., Tindall, E.A., Fleischmann, R.M., Weaver, A.L., Ettlinger, R.E., Cohen, S., Koopman, W.J., Mohler, D., Widmer, M.B., and Blosch, C.M. 1997. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N. Engl. J. Med. 337:141-147.
34. ✓	Ohshima, S. Saeki, Y. Mima, T., Sasai, M., Nishioka, K., Ishida, H., Shimizu, M., Suemura, M., McCloskey, R., and Kishimoto, T. 1999. Long-term follow-up of the changes in circulating cytokines, soluble cytokine receptors, and white blood cell subset counts in patients with rheumatoid arthritis (RA) after monoclonal anti-TNF a antibody therapy. J. Clin. Immunol. 19:305-313.
35. ✓	Kontinen Y.T., Ceponis A., Takagi M., Ainola M., Sorsa T., Sutinen M., Salo T., Ma J., Santavirta S., Seiki M. 1998. New collagenolytic enzymes/cascade identified at the pannus-hard tissue junction in rheumatoid arthritis: destruction from above. Matrix Biol. 17(8-9):585-601.
36. ✓	Little, C.B., Flannery, C.R., Hughes, C.E., Mort, J.S., Roughley, P.J., Dent, C., and Caterson, B. 1999. Aggrecanase versus matrix metalloproteinases in the catabolism of the interglobular domain of aggrecan in vitro. Biochem. J. 344:61-68.
37. ✓	Anderson E.D., Thomas L., Hayflick J.S., Thomas G. 1993. Inhibition of HIV-1 gp160-dependent membrane fusion by a furin-directed alpha1-antitrypsin variant. J. Biol. Chem. 268(33):24887-91.
38. ✓	Pei D. Weiss S.J. 1995. Furin-dependent intracellular activation of the human stromelysin-3 zymogen. Nature 375(6528):244-7.

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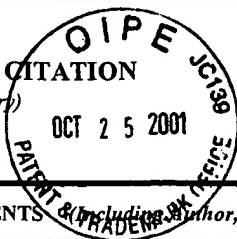
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39.	Jean, F., Stella, K., Thomas, L., Liu, G., Xiang, Y., Reason, A.J., and Thomas, G. 1998. alpha1-Antitrypsin Portland, a bioengineered serpin highly selective for furin: application as an antipathogenic agent. Proc. Natl. Acad. Sci. USA 95:7293-7298.
40.	Cui, Y., Jean, F., Thomas, G., and Chrisian, J.L. 1998. BMP-4 is proteolytically activated by furin and/or PC6 during vertebrate embryonic development. EMBO J. 17:4735-4743.
41.	Watanabe M., Hirano A., Stenglein S., Nelson J., Thomas G., Wong T.C. 1995. Engineered serine protease inhibitor prevents furin-catalyzed activation of the fusion glycoprotein and production of infectious measles virus. J. Virol. 69(5):3206-10.
42.	Hurwitz, D.R., and Chinnadurai, G. 1985. Evidence that a second tumor antigen coded by adenovirus early gene region E1a is required for efficient cell transformation. Proc. Natl. Acad. Sci. USA. 82:163-167.
43.	Mosser D.D., Caron A.W., Bourget L., Jolicoeur P., Massie B. 1997. Use of a dicistronic expression cassette encoding the green fluorescent protein for the screening and selection of cells expressing inducible gene products. Biotechniques 22:150-4, 156, 158-61.
44.	Gossen, M., and Bujard, H. 1992. Tight control of gene expression in mammalian cells by tetracycline-responsive promoters. Proc. Natl. Acad. Sci. USA 89:5547-5551.
45.	Petrof, B.J., Acsadi, G., Jani, A., Massie, B., Bourdon, J., Matusiewicz, N., Yang, L., Lochmuller, H., and Karpati, G. 1995. Efficiency and functional consequences of adenovirus-mediated in vivo gene transfer to normal and dystrophic (mdx) mouse diaphragm. Am. J. Resp. Cell & Mol. Biol. 13:508-517.
46.	Takahashi, S., Nakagawa, T., Kasai, K., Banno, T., Duguay, S.J., Van de Ven, W.J., Murakami, K., and Nakayama, K. 1995. A second mutant allele of furin in the processing-incompetent cell line, LoVo. Evidence for involvement of the homo B domain in autocatalytic activation. J. Biol. Chem. 270:26565-26569.
47.	Hallenberger, S., Bosch, V., Angliker, H., Shaw, E., Klenk, H.D., and Garten, W. 1992. Inhibition of furin-mediated cleavage activation of HIV-1 glycoprotein gp160. Nature. 360:358-361.
48.	Jean F., Stella K., Thomas L., Liu G., Xiang Y., Reason A.J., Thomas G. 1998. alpha1-Antitrypsin Portland, a bioengineered serpin highly selective for furin: application as an antipathogenic agent. Proc Natl Acad Sci USA 23: 7293-8.
49.	Peschon JJ, Slack JL, Reddy P, Stocking KL, Sunnarborg SW, Lee DC, Russell WE, Castner BJ, Johnson RS, Fitzner JN, Boyce RW, Nelson N, Kozlosky CJ, Wolfson MF, Rauch CT, Cerretti DP, Paxton RJ, March CJ, Black RA. 1998. An essential role for ectodomain shedding in mammalian development. Science. 282:1281-4.
50.	Steube K.G., Teepe D., Meyer C., Zaborski M., Drexler H.G. 1997. A model system in haematology and immunology: the human monocytic cell line MONO-MAC-1. Leuk Res. 21:327-35.

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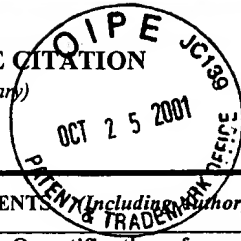
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51.

Lark, M.W., et al. 1995. Quantification of a matrix metalloproteinase-generated aggrecan G1 fragment using monospecific and anti-peptide serum. Biochem J. 307:245-252.

52.

Lark, M.W. et al. 1995. Cell-mediated catabolism of aggrecan. Evidence that cleavage at the aggrecanase site (Glu373-Ala374) is a primary event in proteolysis of the interglobular domain. J. Biol. Chem. 270:2550-2556.

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